Beneficence and Non-maleficence for Pediatric Research that Poses More than Minimal Risk and Uncertain Benefit

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2002 OHRP Review of Protocol Smallpox Vaccine in Children

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Smallpox Vaccine in U.S. General Population

- 1800's – 1972 Universal for ≥1 year
- 1972 Vaccine risks > risk smallpox
- 1980 Smallpox declared eradicated
- 2001 9/11, Anthrax, Fear of additional bioterrorism

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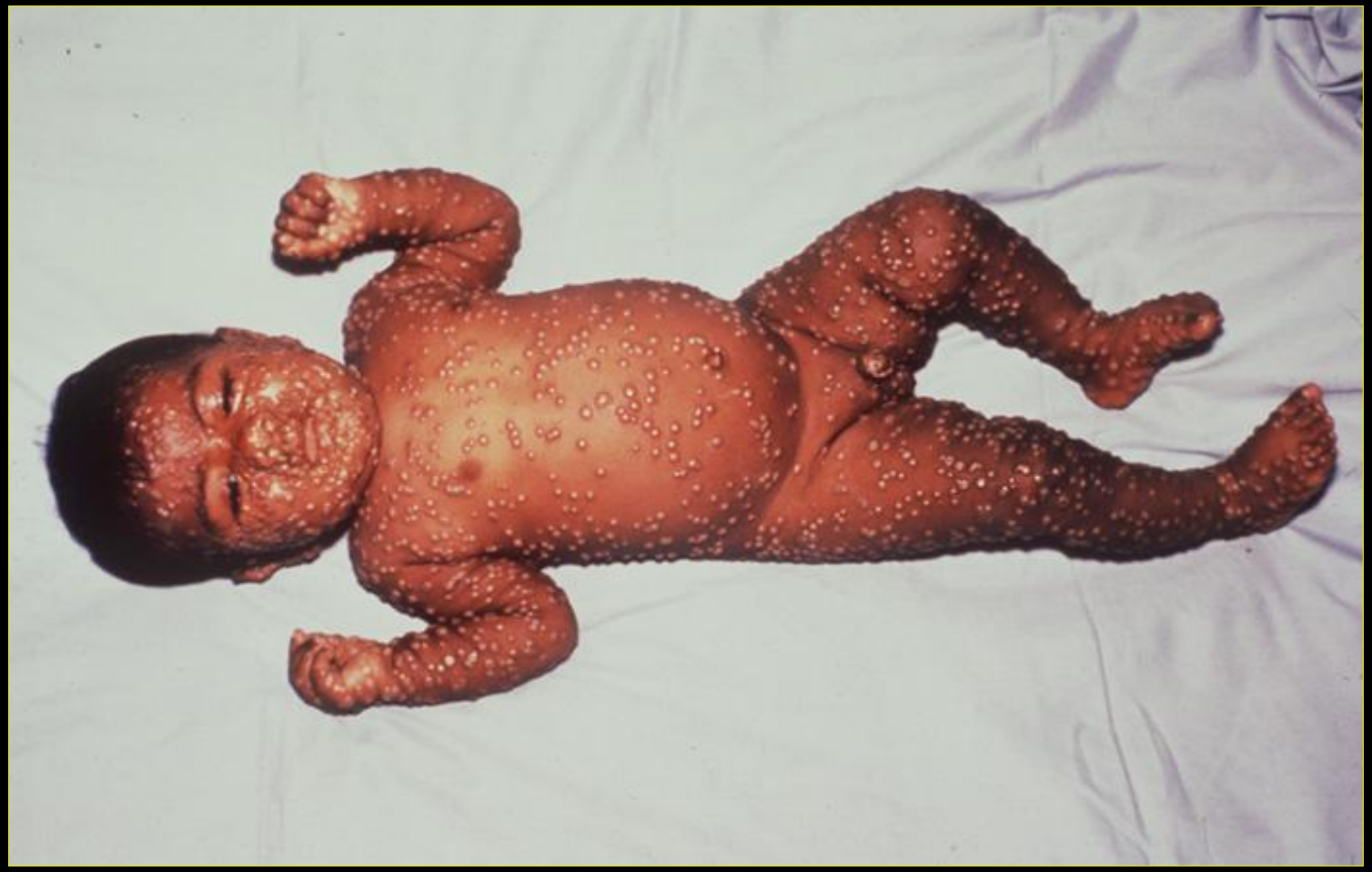
Variola Major



30% Case-fatality rate

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Bioterrorism Exercise

Center for Biosecurity UPMC

DARK WINTER

Exercise Site Map | Home

- Overview
- Summary
- Findings
- Exercise Script (PDF)
- Briefing Slides

Exercise developed and produced by:

Johns Hopkins Center for

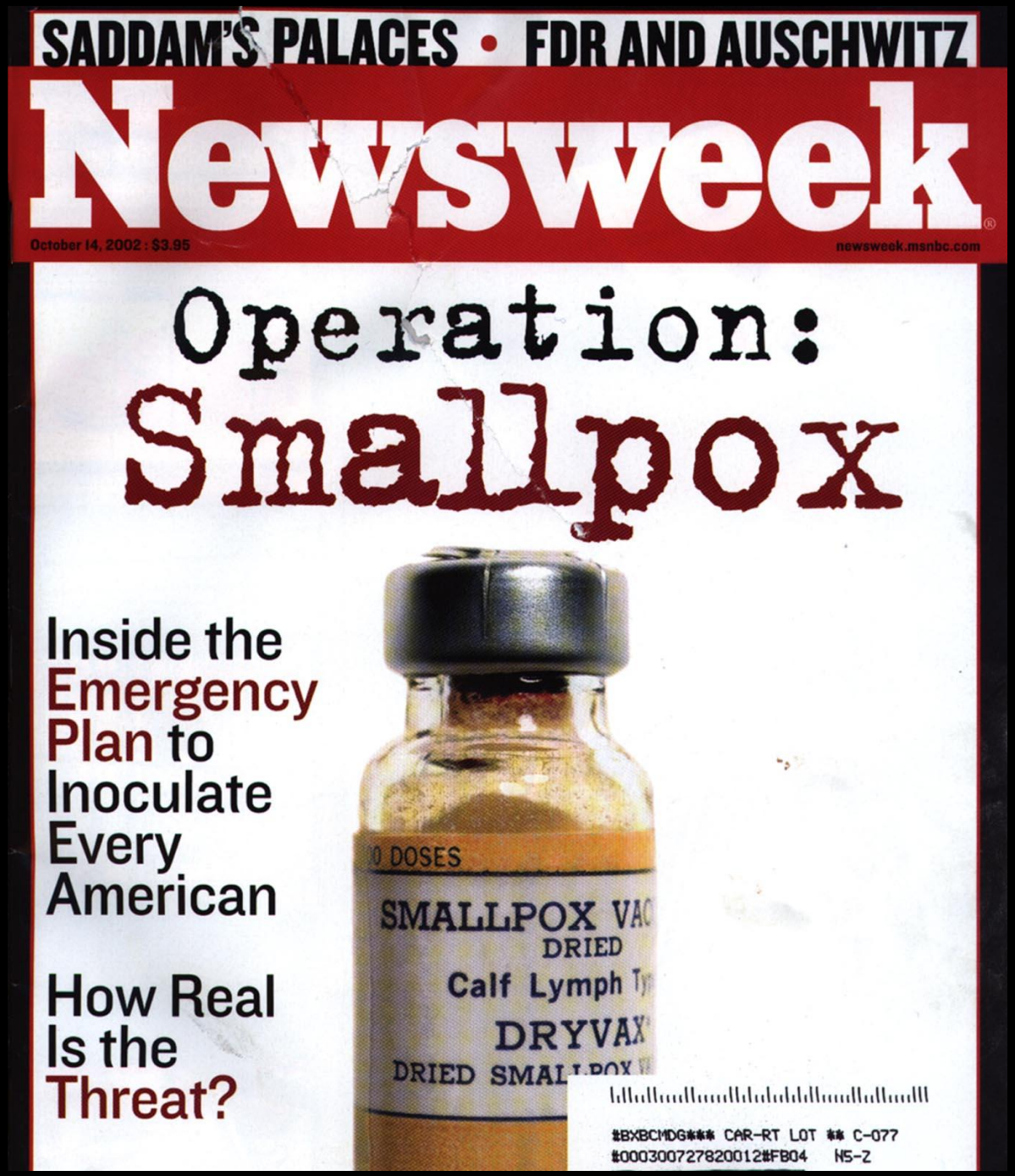
Home > Events > Dark Winter.

Exercise Overview

June 22-23, 2001

The *Dark Winter* exercise portrayed a *fictional* scenario depicting a covert smallpox attack on U.S. citizens. The scenario is set in three successive National Security Council (NSC) meetings (Segments 1,2 and 3) which take place over a period of 14 days. Former senior government officials played the roles of NSC members responding to the evolving epidemic; representatives from the media were among the observers of these mock NSC meetings and played journalists during the scenario's press conferences (see Players List). The exercise itself was held at Andrews Air Force Base, Washington, D.C., on June 22-23, 2001.

Dec 2001 survey:
75% of adults
would take vaccine



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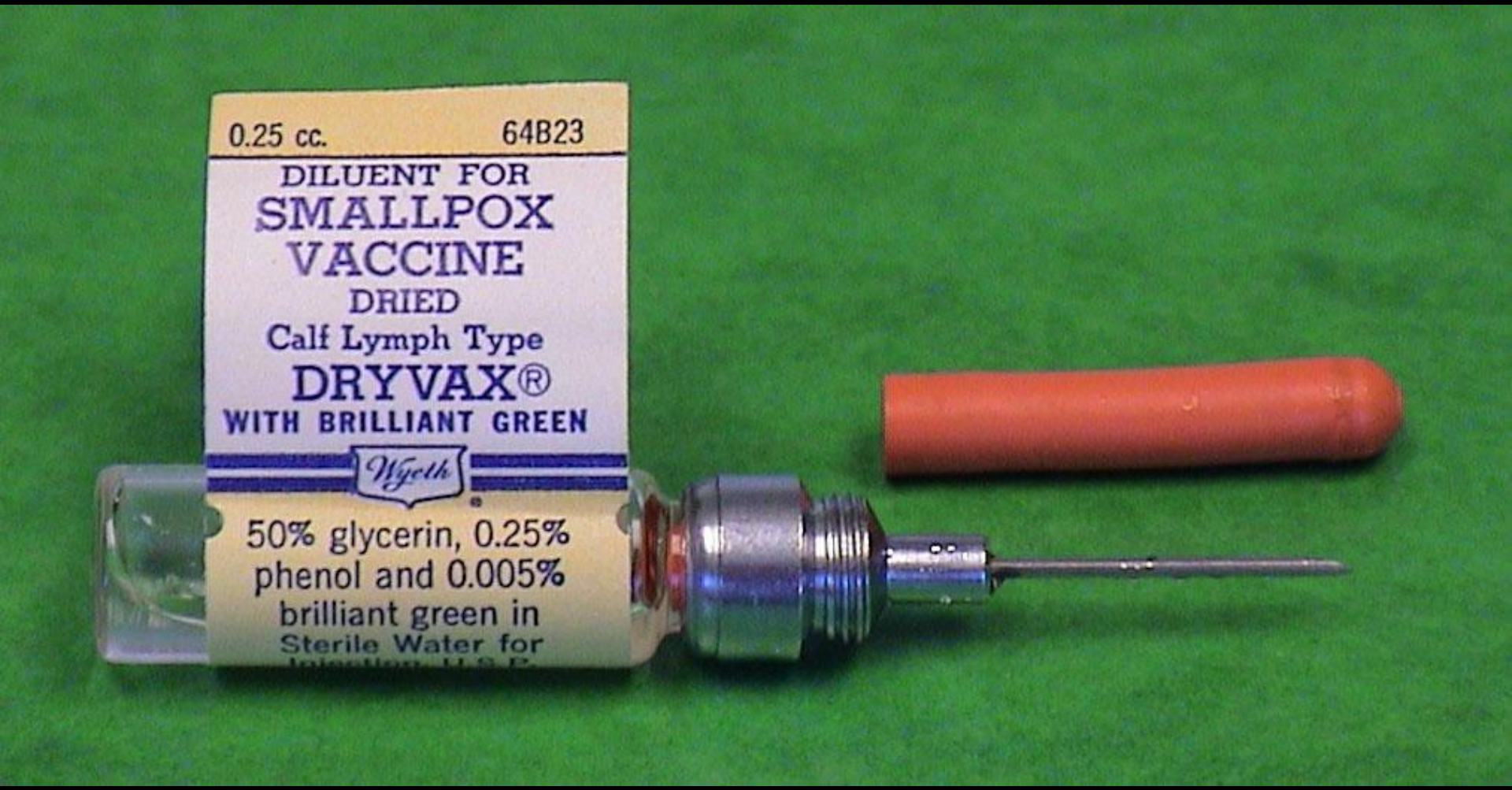
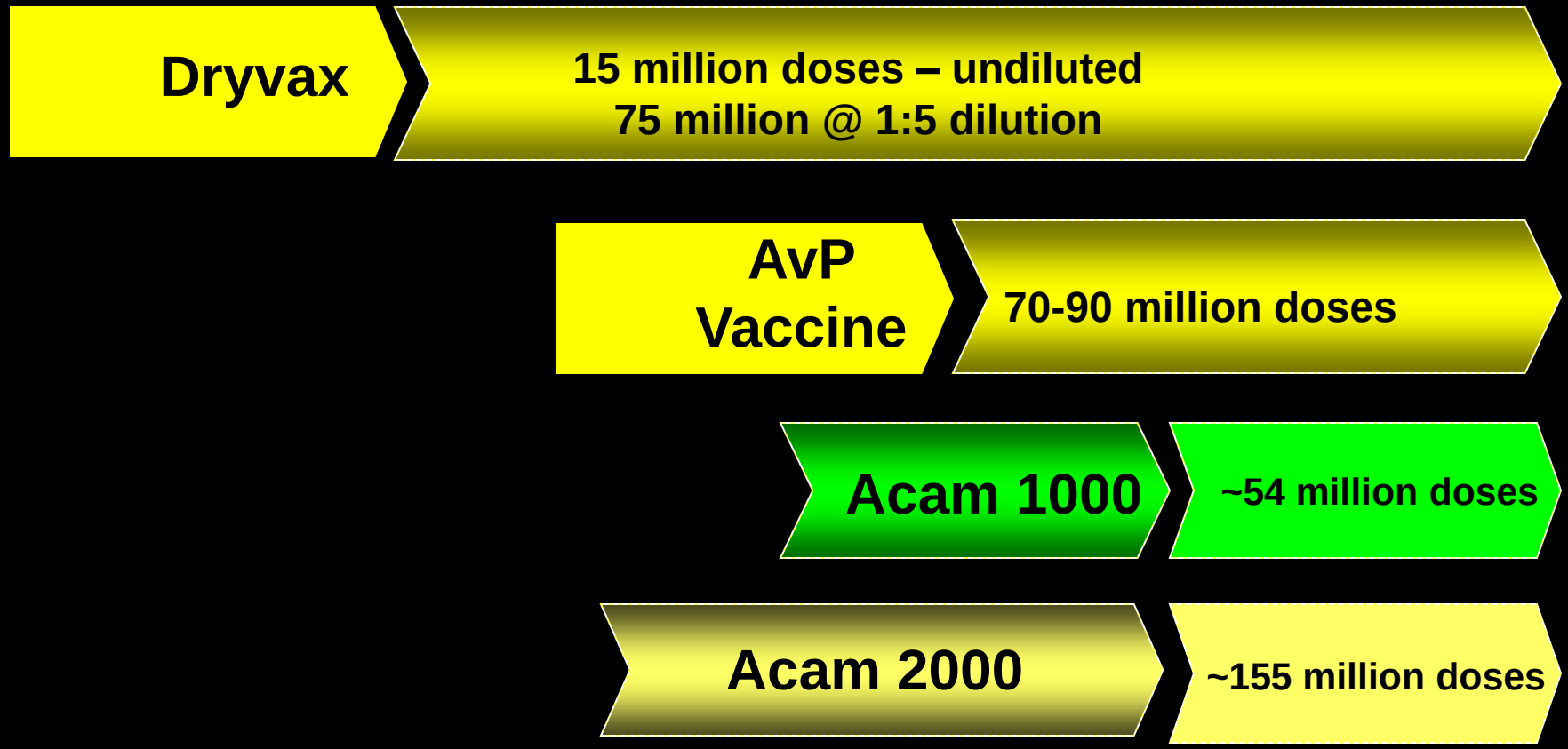
Original Diluent



Smallpox Vaccine Supply and Production



Orenstein and Margolis

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CDC

Response to Smallpox Vaccine by Dilution in Adults

Dilution	No. Vac	% Responding
Undiluted	106	97.2 (92.0-99.4)
1:5	234	99.1 (97.0-99.9)
1:10	340 680	97.1 (94.7-98.6)

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Frey et al NEJM 2002; 346: 1265-74

A Multicenter, Randomized, Dose Response Study of the Safety, Clinical and Immune Responses of Dryvax Administered to Children 2 to 5 Years of Age

- Protocol prepared June 2002
- Sponsor: National Institutes of Health
- Under FDA IND
- 40 children: 20 undiluted, 20 diluted 1:5
- Compare “take” rates and side effects

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Approved by IRBs at Cincinnati Children’s and Kaiser Permanente

Harbor UCLA IRB Review

- CFR 46.405:
  - 5 for, 5 against, 1 abstention
  - Chair voted to break tie - 6 against
- CFR 46.407
  - 11 for, 0 against
- Aug 5, 2002 Referred to Secretary HHS

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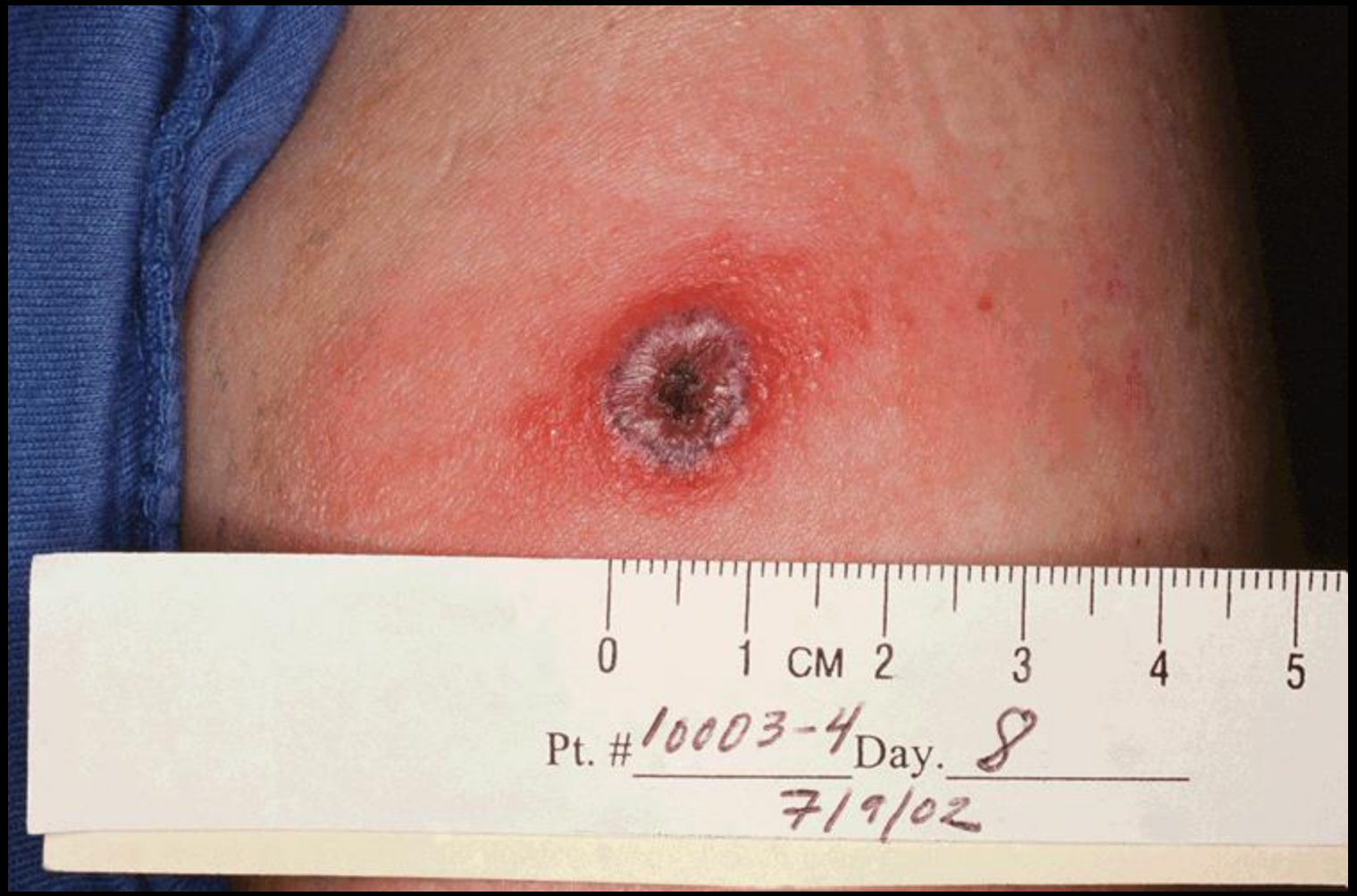
Smallpox Vaccine Day 8



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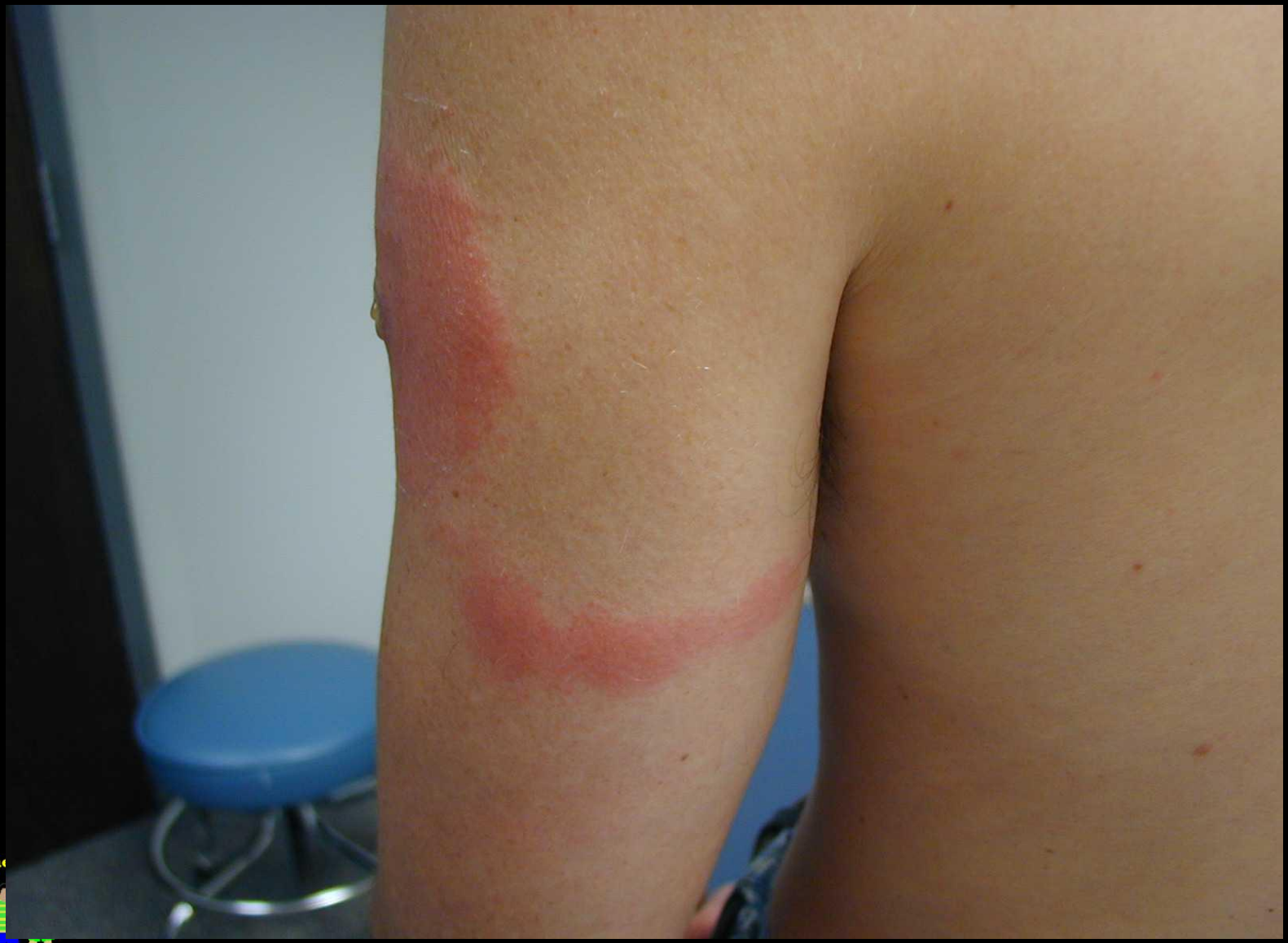
Robust Take



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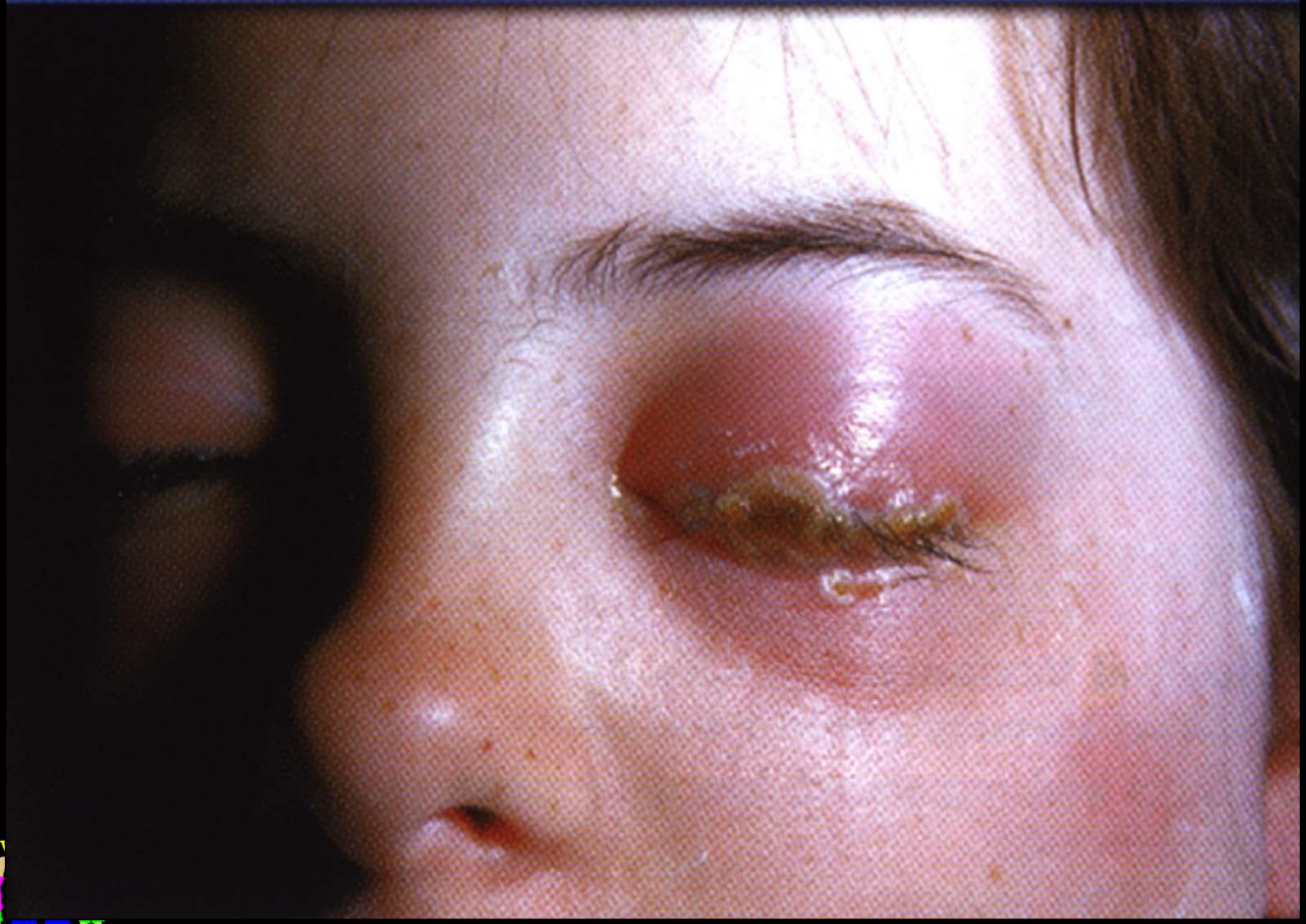
Robert B. Belshe

Adverse Reactions: **Accidental Implantation**



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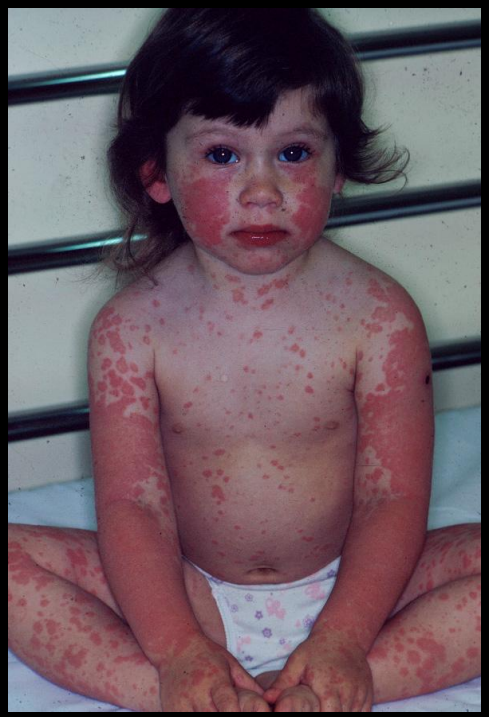
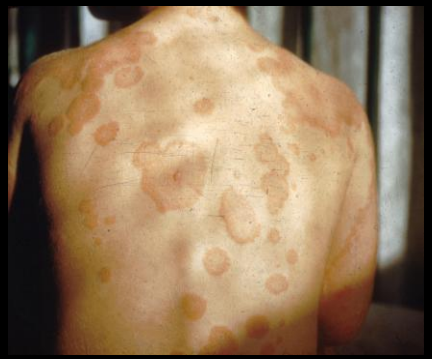
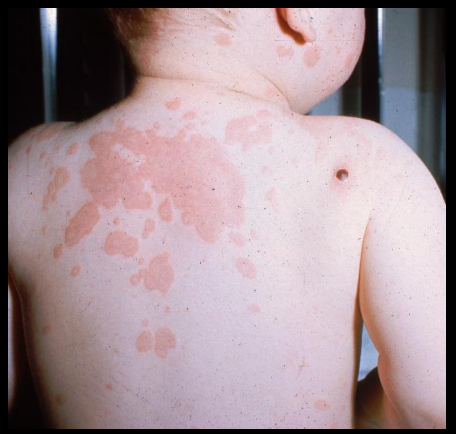
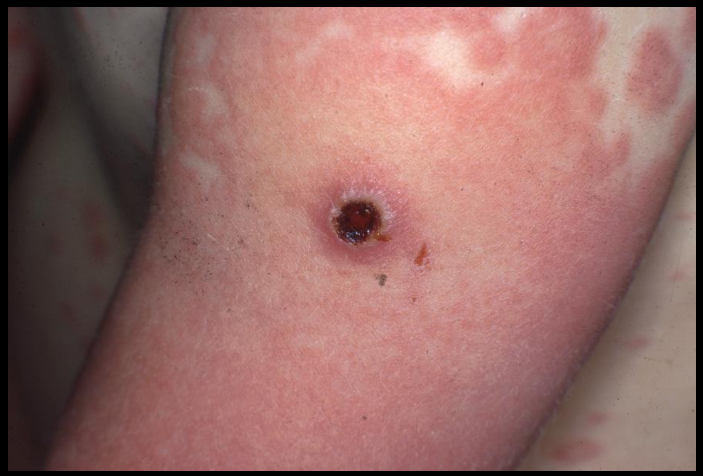
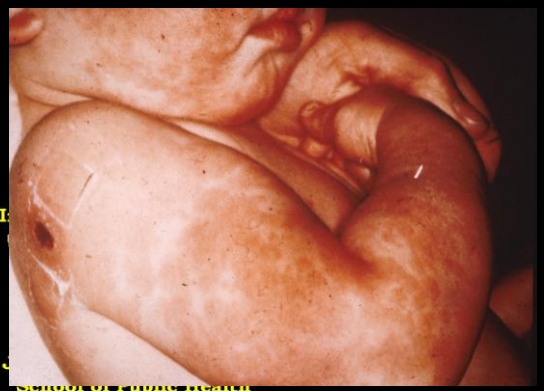


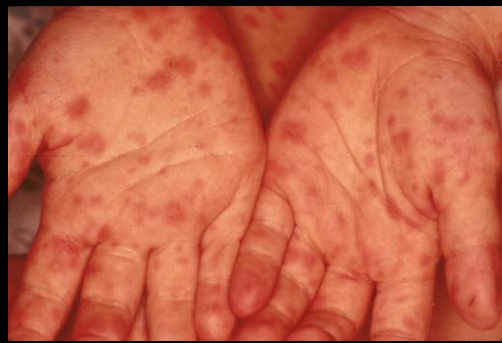






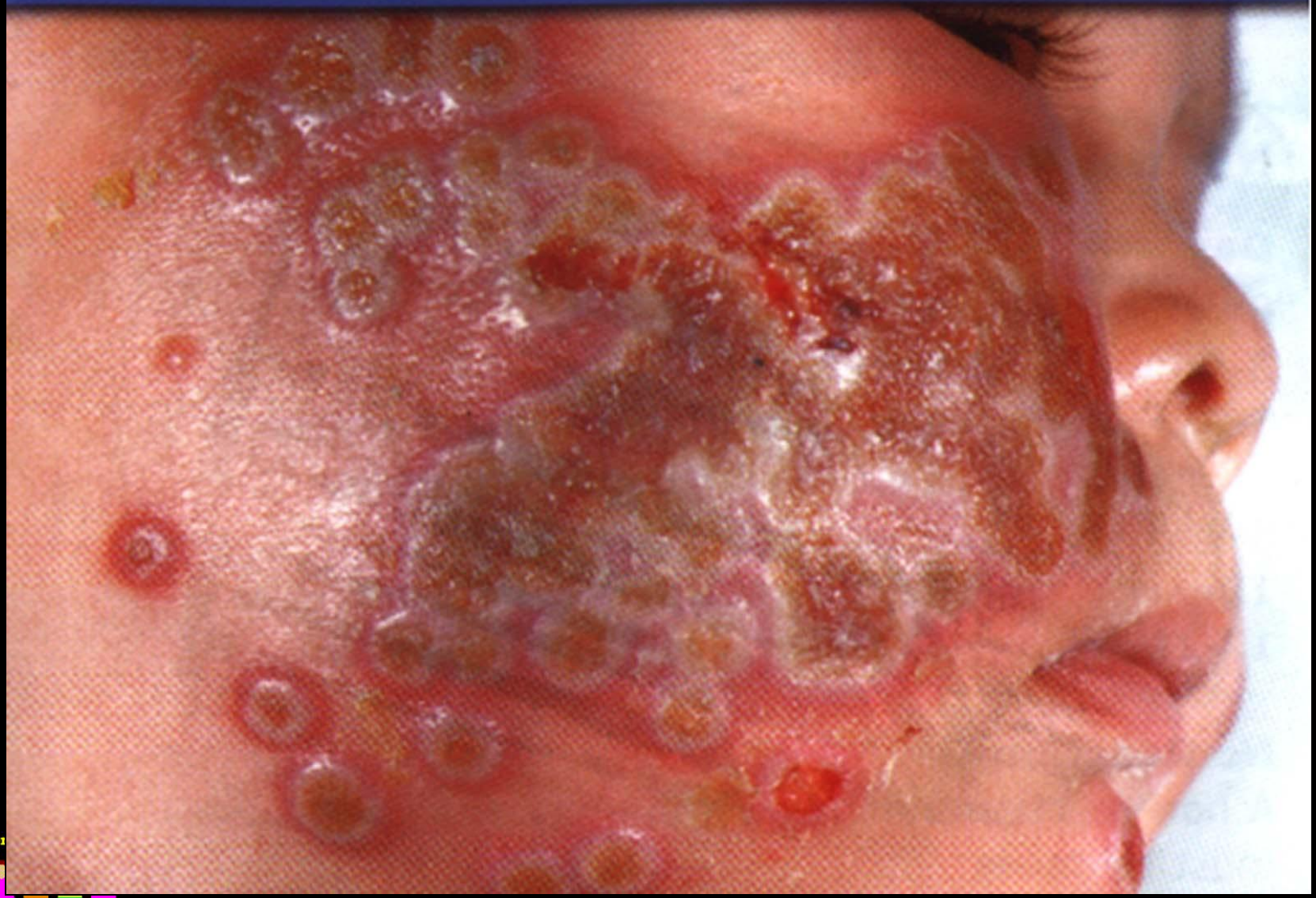
COMMON, IMPRESSIVE, BUT BENIGN; RARELY CAN SEE STEVENS-JOHNSON SYNDROME



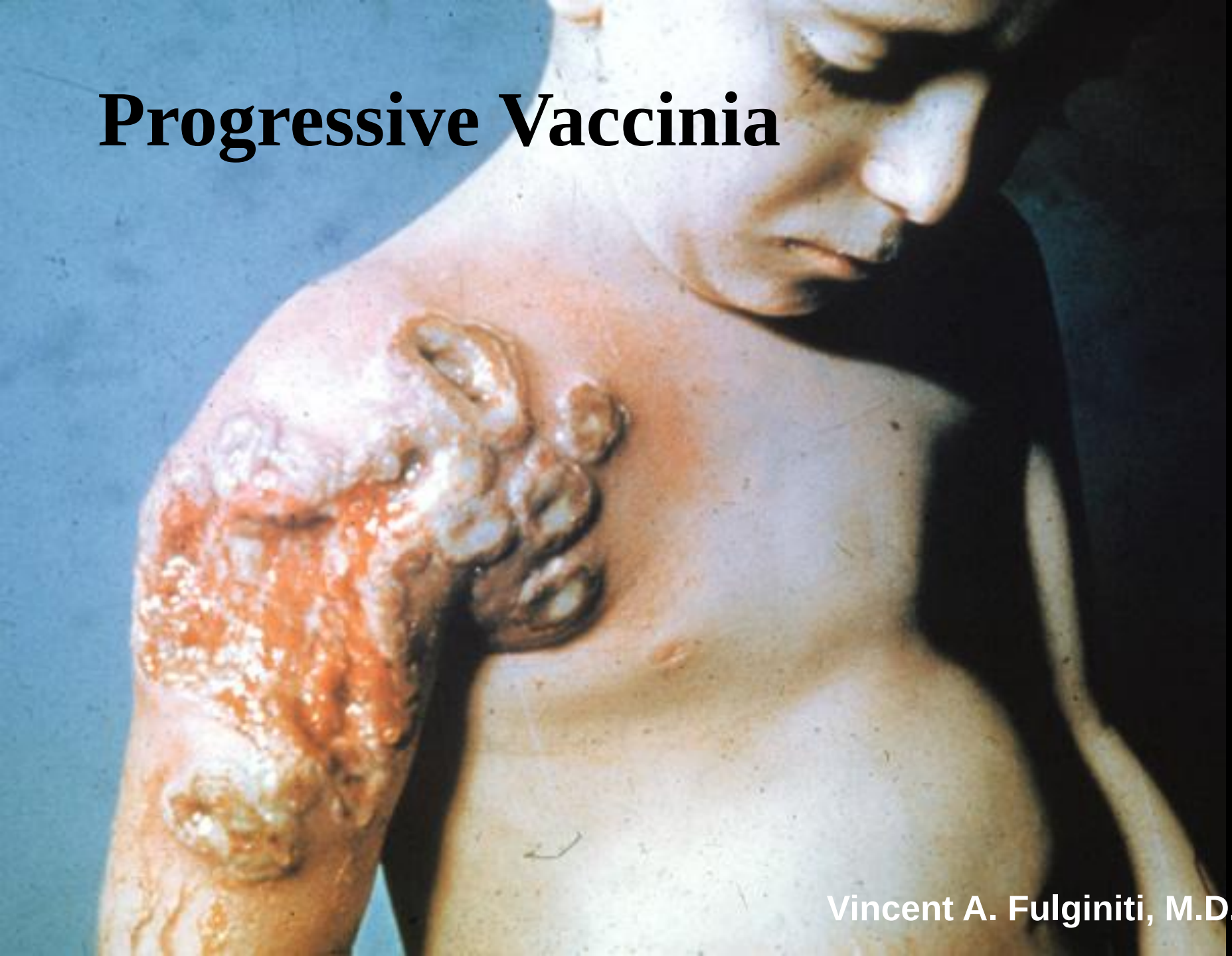


Vincent A. Fulginiti, M.D.

Adverse Reactions: **Eczema Vaccinatum**



Progressive Vaccinia



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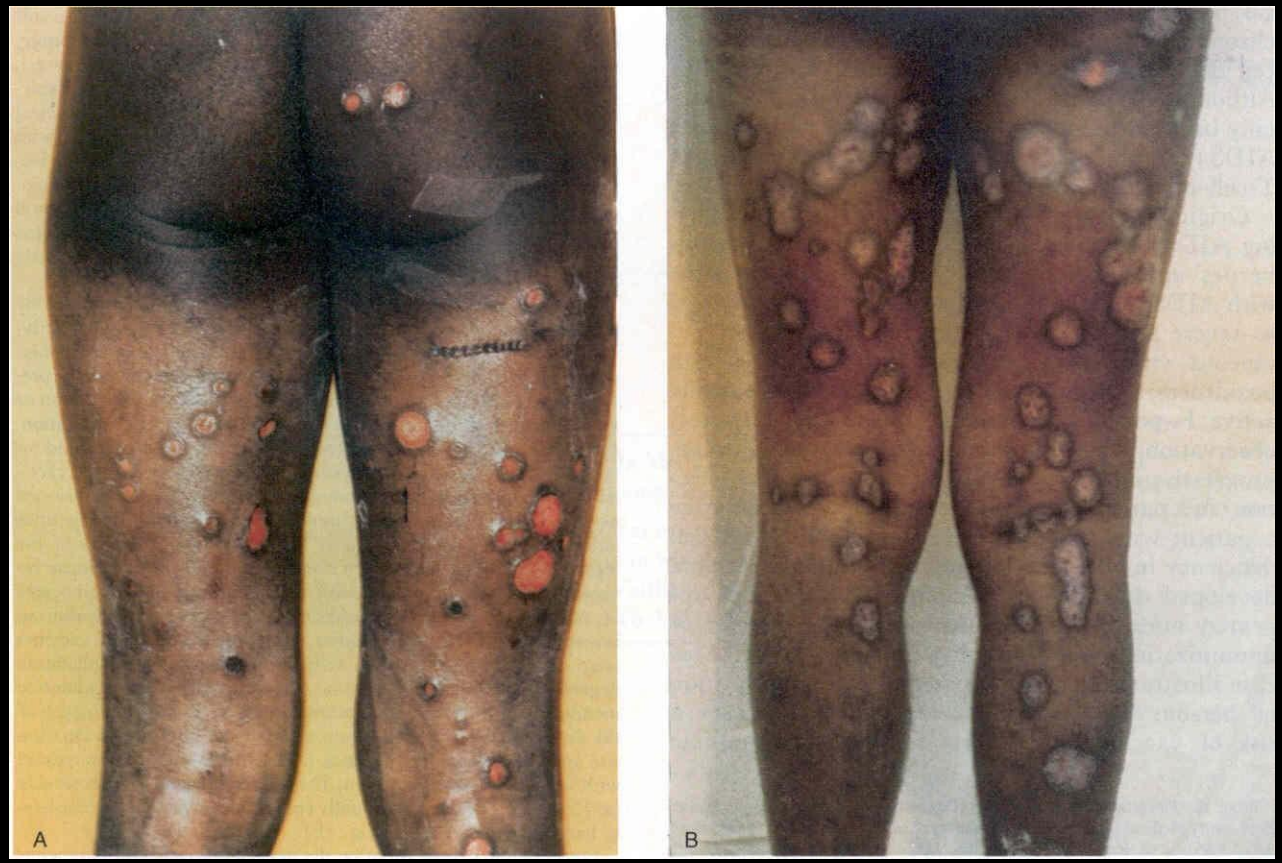
Disseminated Vaccinia 1 Month after Vaccination in HIV Infected Recruit



Lesions during the first week of disseminated disease (day 5)

Extensive scarring of the resoling lesions after 9 weeks of passive immunotherapy.

Source: Redfield. NEJM 1987;316(11):673-6.

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Complications* from Smallpox Vaccine 10 State Survey 1968

Age	<1	1-4	5-9	≥20	TOTAL
Inadvertent inoculation	507	577	371	606	529
Generalized vaccinia	394	233	140	212	242
Eczema vaccinatum	14	44	35	30	39
Progressive vaccinia	-	3	-	-	2
Encephalitis	42	10	9	-	12
Death	5	1	1	?	-

* Per million primary vaccinations

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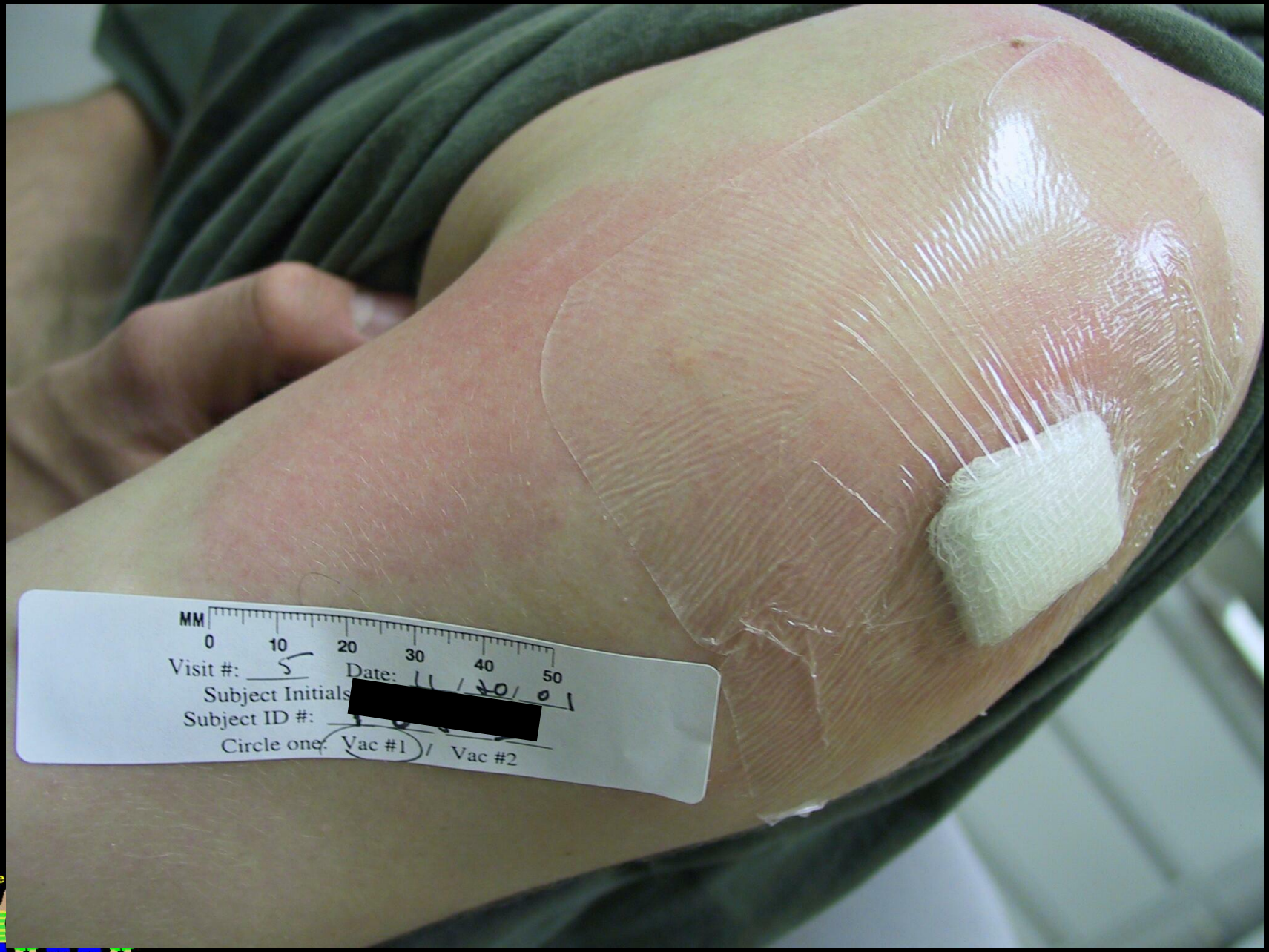
Lane JM J Infect Dis 1970; 122:303



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Adverse Events Following Smallpox Vaccination* Among 665 Healthy Adults 18-32 Year Old Adults

Event	Percent
Temp ≥ 101^{o}	3.0
Erythema >10 cm	10.0 (mean =51mm)
HA mod-severe	13.9
Rash	14.3
Pain mod-severe	33.9
Missed work/school/ recreation	36.5

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*Most received a reduced dose

Frey et al NEJM 2002; 346: 1265-74

2002 Pediatric Protocol Review Issues

- Risk understated:
  - Encephalitis risk is higher in children
  - Serious complications not “remote”
  - Transmission
- Potential benefit overstated
- Consent from both parents
- Safety monitoring
- Alternatives

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Non-maleficence

- Careful screening
- Minimize Exposure
- Undiluted vaccine known to result in high take rates in children
- Study diluted vaccine first: if high take rate, no need to expose additional children to undiluted vaccine

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Beneficence

- Select children whose parents have received smallpox vaccine:
  - Maximize parental knowledge of vaccine
  - For parents working in laboratories with the vaccine, some theoretical potential for inadvertent exposure

45 CFR 46.404, 405, 406, and 407

- Not approvable under 404, 405, or 406
- CFR 46.407
  - Greater than minimal risk, no or uncertain benefit
  - Reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children

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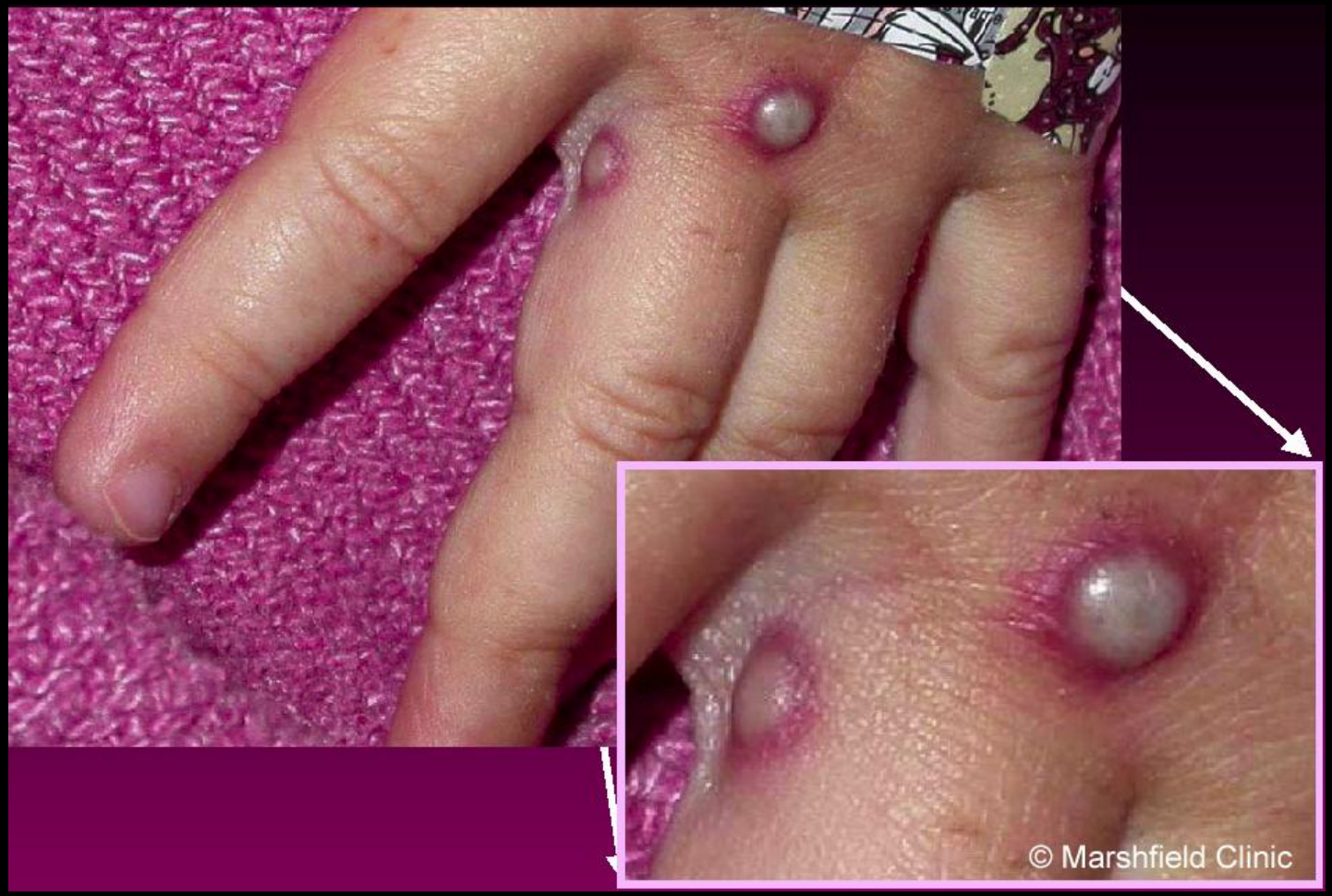
Since initiating this regulatory review process, bioterrorism preparedness plans have evolved such that, under current plans, the potential to use diluted Dryvax® in children will no longer exist. In the absence of plans to use diluted Dryvax® in children, the Secretary, HHS, and the Commissioner, FDA, have determined that there is no justification for this particular clinical investigation to proceed. Please note that this determination applies only to the above-referenced study involving Dryvax® in children, and does not pertain to future research involving smallpox vaccines in children.

Statement issued January 25, 2003 from Secretary and Commissioner

Monkeypox in a Child
Wisconsin 5/27/03

Smallpox Vaccine given to exposed children and adults



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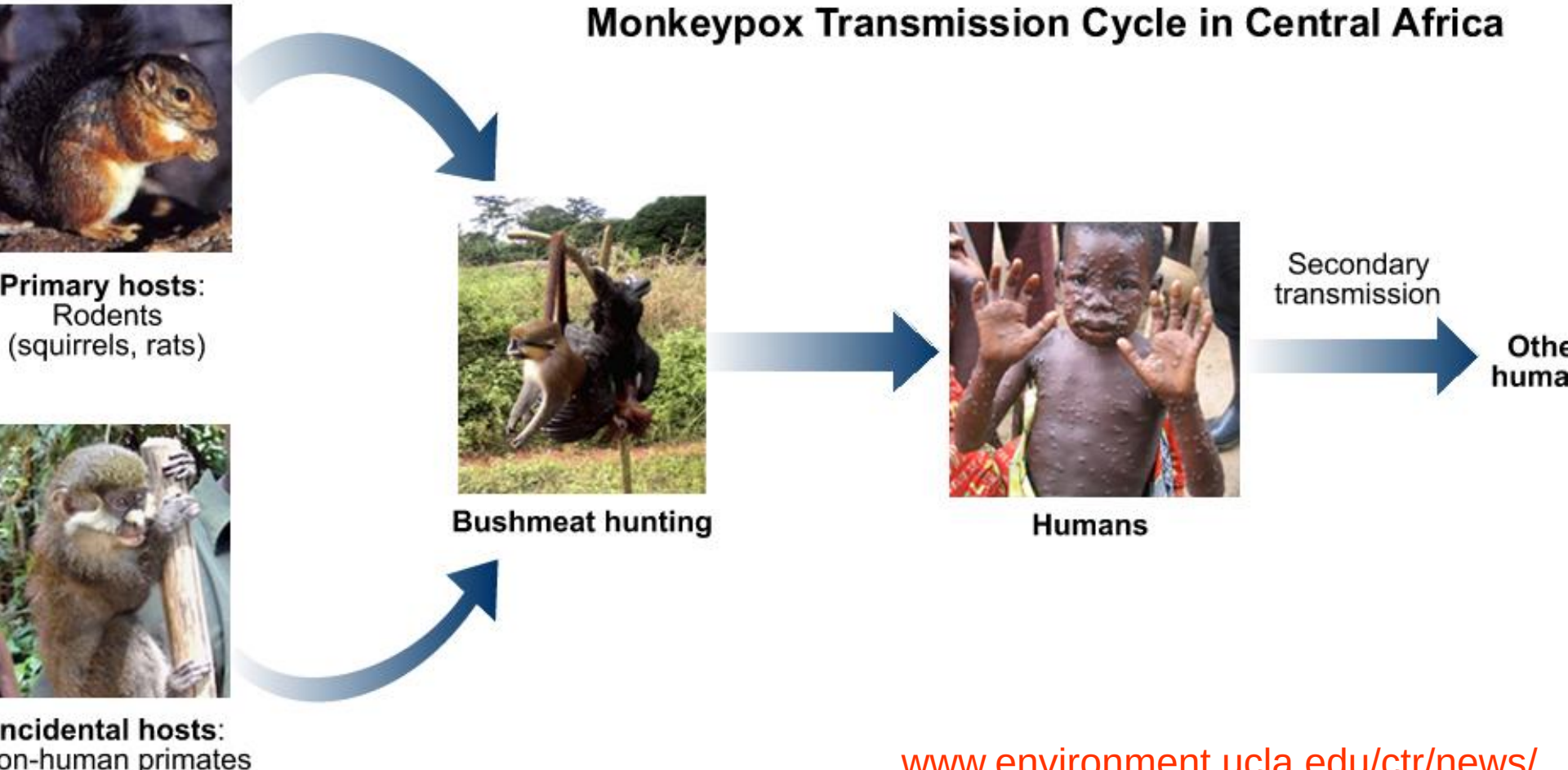
Joanne Cono

http://research.marshfieldclinic.org/crc/files/MonkeyPox_MarshfieldWI_ClinicalPhotos_v3.pdf

Monkeypox is Preventable with Smallpox Vaccine



www.environment.ucla.edu/ctr/news/

Developments Since 2002

- Myocarditis risk ~1/10,000
- Dryvax not available
- ACAM2000 licensed
- MVA?- in stockpile, not licensed

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What Constitutes Sufficient Estimated Risk to Justify Studies in Children for Countermeasures?

- Pediatric Rule: Need to study vaccines and drugs in children when there is anticipated use in children

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OHRP Website
Reviewers Comments

www.hhs.gov/ohrp/archive/children/dryvax.html